



(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention  
of the grant of the patent:  
**03.01.2001 Bulletin 2001/01**

(51) Int Cl.<sup>7</sup>: **C07D 473/00**

(21) Application number: **89307271.0**

(22) Date of filing: **18.07.1989**

(54) **Process for the preparation of purine derivatives**

Verfahren zur Herstellung von Purinderivaten

Procédé pour la préparation de dérivés de purine

(84) Designated Contracting States:  
**AT BE CH DE ES FR GB GR IT LI LU NL SE**

(30) Priority: **23.07.1988 GB 8817607**

(43) Date of publication of application:  
**31.01.1990 Bulletin 1990/05**

(73) Proprietor: **BEECHAM GROUP PLC**  
**Brentford, Middlesex TW8 9EP (GB)**

(72) Inventors:  
• **Grinter, Trevor John,**  
**SmithKline Beecham Pharmaceu**  
**Tonbridge Kent TN11 9AN (GB)**  
• **Kincey, Peter Markham,**  
**SmithKline Beecham Pharmace**  
**rbour Road, Harlow Essex CM19 5AD (GB)**

(74) Representative: **Tocher, Pauline et al**  
**SmithKline Beecham plc**  
**Corporate Intellectual Property,**  
**Two New Horizons Court**  
**Brentford, Middlesex TW8 9EP (GB)**

(56) References cited:  
**EP-A- 0 141 927 EP-A- 0 182 024**  
**EP-A- 0 302 644 WO-A-87/05604**

Remarks:

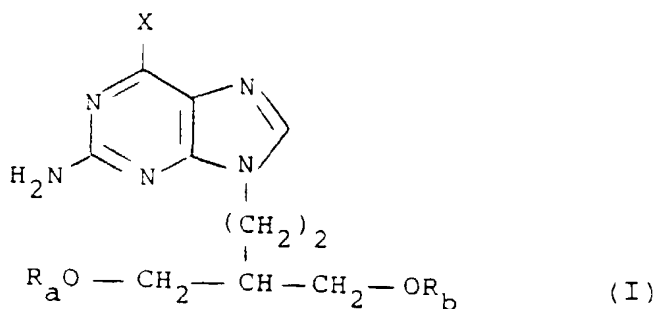
The file contains technical information submitted  
after the application was filed and not included in this  
specification

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

## Description

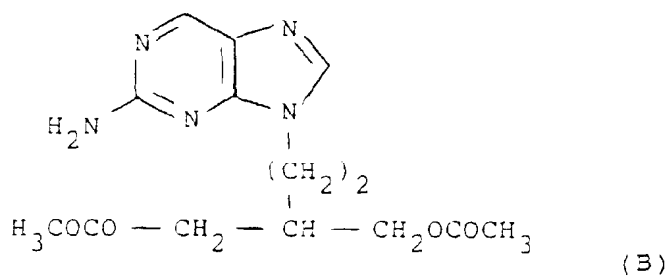
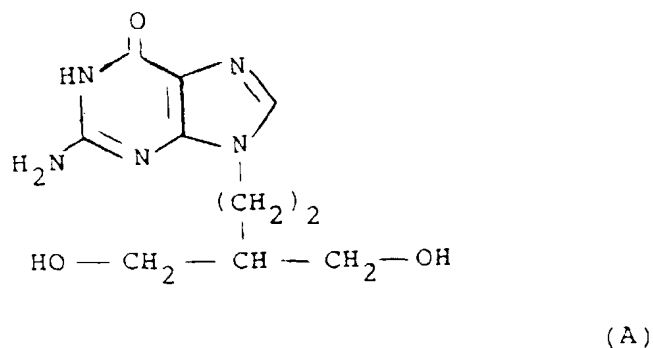
[0001] The present invention relates to a novel process for the preparation of purine derivatives which have antiviral activity.

[0002] EP-A-141927 and EP-A-182024 (Beecham Group p.l.c.) describe, *inter alia*, compounds of formula (I) and pharmaceutically acceptable salts thereof:

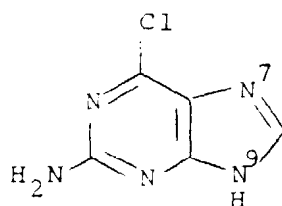


wherein X is hydrogen or hydroxy and  $\text{R}_a$  and  $\text{R}_b$  are independently hydrogen or a group  $\text{RCO}-$  wherein R is phenyl or  $\text{C}_{1-18}$  alkyl.

[0003] The compounds of formulae (A) and (B); wherein X is OH and  $\text{R}_a$  and  $\text{R}_b$  are both hydrogen (BRL 39123); and wherein X is hydrogen and  $\text{R}_a$  and  $\text{R}_b$  are both acetyl (BRL 42810), are of particular interest as potential antiviral agents.

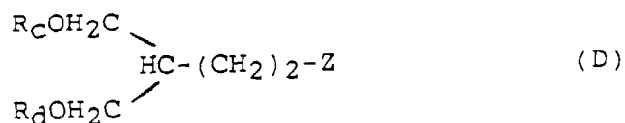


[0004] The process already described for the preparation of the above compounds involves the reaction of 2-amino-6-chloropurine of formula (C):



(C)

with a side chain intermediate of formula (D):



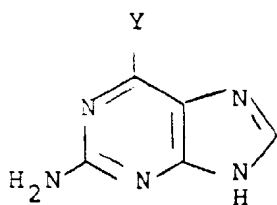
(D)

wherein  $R_c$  and  $R_d$  are independently acyl groups or hydroxy protecting groups and Z is a leaving group, such as halo, for example chloro, bromo, iodo; and thereafter converting the 6-chloro group to hydroxy by means of hydrolysis, or to hydrogen by means of reduction.

**[0005]** The disadvantage with this process is that the use of the intermediate of formula (C) results in a mixture of products i.e. that when the side chain is attached at N-9 and the undesired product wherein the side chain is attached at N-7. This can result in low yields of the desired N-9 product.

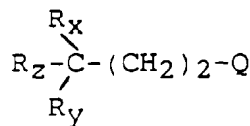
**[0006]** It has surprisingly been discovered that, if the 6-chloro group in the compound of formula (C) is replaced by an iodo group, a diphenylmethylthio or a benzylthio group wherein the phenyl moiety is optionally substituted by one or two groups selected from  $C_{1-4}$  alkyl, halo and  $C_{1-4}$  alkoxy, the ratio of N-9 product to N-7 product is increased, providing a better overall yield of the resulting compound of formula (I).

**[0007]** Accordingly, the present invention provides a process for the preparation of a compound of formula (I) as hereinbefore defined, or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (II):



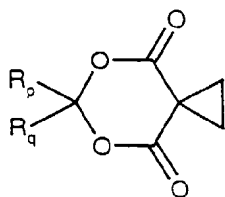
(II)

wherein the amino group is optionally protected, Y is iodo, diphenylmethylthio or benzylthio wherein the phenyl moiety is optionally substituted by one or two groups selected from  $C_{1-4}$  alkyl, halo and  $C_{1-4}$  alkoxy, with a compound of formula (III):



(III)

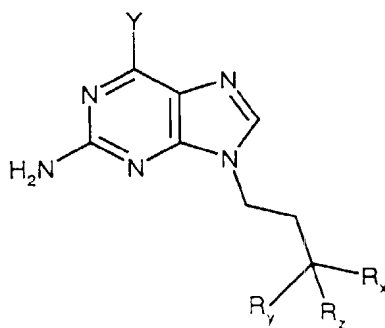
wherein Q is a leaving group,  $R_x$  and  $R_y$  are protected hydroxymethyl or acyloxymethyl, or group(s) convertible to hydroxymethyl or acyloxymethyl; and  $R_z$  is hydrogen or a group convertible thereto; or a compound of formula (IIIA):-



(IIIA)

wherein  $R_p$  and  $R_q$  are independently hydrogen,  $C_{1-6}$ alkyl or phenyl, or  $R_p$  and  $R_q$  together are  $C_{4-6}$  polymethylene; and thereafter converting Y to X is hydroxy by means of hydrolysis, or to X is hydrogen by means of reduction; converting  $R_x$  and  $R_y$ , when other than hydroxymethyl or acyloxymethyl, to hydroxymethyl or acyloxymethyl, optionally converting  $R_x/R_y$  hydroxymethyl to acyloxymethyl or vice versa, deprotecting the 2-amino group where necessary and converting  $R_z$ , when other than hydrogen, to hydrogen; and optionally forming a pharmaceutically acceptable salt thereof.

**[0008]** The intermediates formed in this reaction are of formula (IV):



(IV)

which are novel and form an aspect of the invention.

**[0009]** The reaction may be carried out in an inert solvent, for example dimethylformamide, dimethylsulphoxide or acetonitrile, preferably dimethylformamide, in the presence of an inorganic or organic base, over a temperature range from 0°C to the boiling point of the solvent, usually 30-40°C. Examples of inorganic bases include alkali metal hydrides, alkali metal carbonates such as sodium or potassium carbonate and preferably potassium carbonate. Suitable organic bases are 1,8-diazabicyclo[5.4.0]undec-7-ene and tetramethyl guanidine.

**[0010]** Suitable examples of optional substituents in the phenyl group Y when benzylthio are one or two groups selected from  $C_{1-4}$  alkyl, halo and  $C_{1-4}$  alkoxy. Halo includes iodo, bromo, chloro and fluoro, and alkyl/alkoxy groups include those containing methyl, ethyl, n- and iso-propyl. Y may also be diphenylmethylthio, optionally substituted in the phenyl ring(s) as defined for Y when benzylthio. Y is preferably iodo or benzylthio, most preferably iodo.

**[0011]** Suitable examples of the leaving group Q, include halo, such as chloro, bromo or iodo, and tosyloxy and mesyloxy.

**[0012]** Suitable examples of hydroxy protecting groups (other than acyl groups) include the t-butyl dimethylsilyl group removable by 80% acetic acid at elevated temperatures, around 90°C, or by treatment with tetrabutyl ammonium fluoride in a solvent, such as tetrahydrofuran, at ambient temperature.

**[0013]** Another suitable protecting group is wherein the two hydroxy groups in formula (III) (when  $R_x$  is hydroxymethyl) are reacted with 2,2-dimethoxypropane, forming a 1,3-dioxan ring. This group may be removed by acidic hydrolysis.

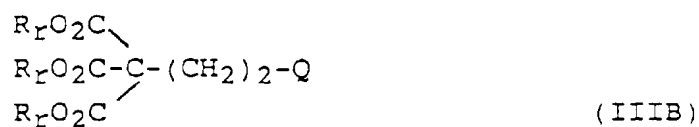
**[0014]** Other suitable protecting groups include substituted benzyl groups such as p-methoxybenzyl, removable by treatment with 2,3-dichloro-5,6-dicyanobenzoquinone.

**[0015]** Other suitable protecting groups are apparent to those skilled in the art.

**[0016]**  $R_x$  and/or  $R_y$  may be acyloxymethyl, such as a group  $RCO_2CH_2$  wherein R is as defined in formula (I). Examples of R include methyl, ethyl, n- and iso-propyl, n- and iso-, sec- and tert-butyl, preferably methyl.

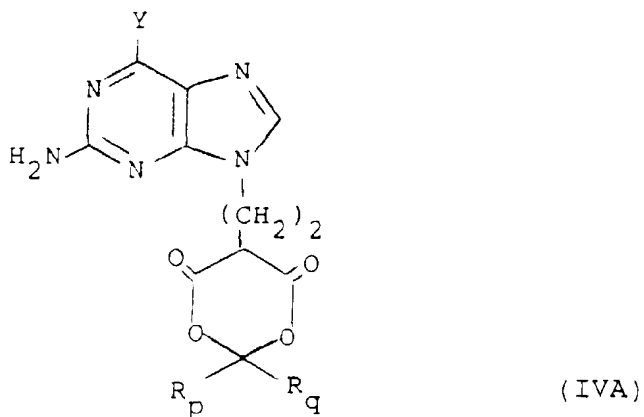
**[0017]** Interconversion of  $R_x/R_y$  acyloxymethyl and hydroxymethyl may be carried out conventionally as described in EP-A-141927.

**[0018]** Other suitable values of  $R_x$ ,  $R_y$ ,  $R_z$  include wherein the compound of formula (III) is of formula (IIIB):

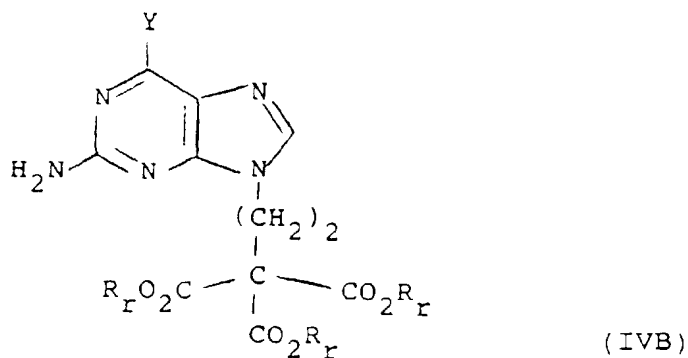


wherein  $R_r$  is  $C_{1-6}$  alkyl or phenyl  $C_{1-6}$  alkyl, in which any phenyl moieties are optionally substituted, (as defined for Y hereinbefore when thiobenzyl).

[0019] When the compound of formula (IIIA) is used, the resulting intermediate is of formula (IVA):

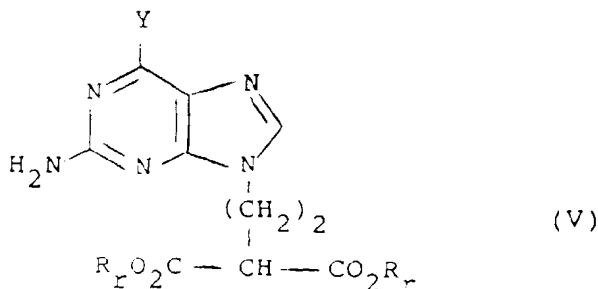


[0020] When the compound of formula (IIIB) is used, the resulting intermediate is of formula (IVB):



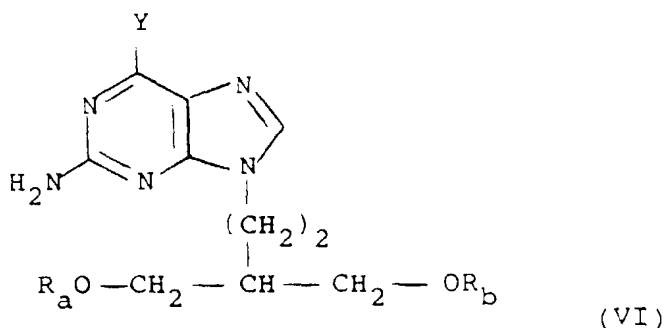
[0021] Values for  $R_p$  and  $R_q$  and  $R_r$  include these values listed as suitable for R in formula (I), preferably methyl for  $R_p$  and  $R_q$  and ethyl for  $R_r$ . In addition  $R_p$  and  $R_q$  may together be  $C_4$  or  $C_5$  polymethylene.

[0022] The intermediates of formulae (IVA) and (IVB) are subsequently converted to an intermediate of formula (V):



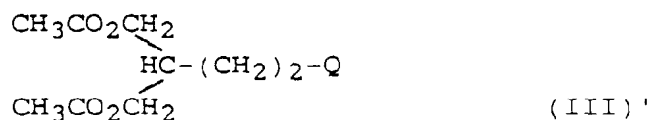
by transesterification and hydrolysis/decarboxylation respectively, as described in the Examples hereinafter.

15 **[0023]** An intermediate of formula (V) is convertible to a compound of formula (VI):



30 by reduction, under conventional conditions using, for example, sodium borohydride.

**[0024]** It is preferred, however, that the intermediate of formula (III) is of formula (III)':



for the preparation of compounds of formula (A) and (B) as defined, because:

45 i) Compounds of formula (III)' give a particularly good N9:N7 ratio (regioselectivity).

ii) Ease of separation of N9:N7 isomers.

(iii) The same intermediate of formula (III)' is used for the preparation of compounds of the formula (A) and formula (B).

50 **[0025]** The 2-amino group may be protected, for example, using a benzyl protecting group, removable by hydrogenolysis. It may also be protected by an acyl group, for example acetyl, removable by hydrolysis, or a Schiff's base, e. g. benzylidene, removable by acid hydrolysis.

**[0026]** Pharmaceutically acceptable salts are formed conventionally.

**[0027]** Intermediates of formula (III) wherein R<sub>x</sub>/R<sub>y</sub> are protected hydroxymethyl or acyloxymethyl may be prepared as described in EP-A-141927 or by analogous methods thereto.

55 **[0028]** Intermediates of the formula (IIIA) are known or are prepared by analogous methods, such as that described in Organic Syntheses Vol 60, page 66.

**[0029]** Intermediates of formula (IIIB) are known or prepared by analogous methods. The compound of formula (IIIB) wherein Q is bromo and R<sub>i</sub> is ethyl may be prepared from triethyl methanetricarboxylate according to the procedure

described by H. Rapoport et.al., J. Org. Chem., 44, 3492(1979).

[0030] Intermediates of the formula (II) wherein Y is iodo or a benzylthio group may be prepared from the compound of formula (C). When Y is iodo, the preparation is by reaction with HI in a transhalogenation reaction, preferably using a cosolvent, such as acetone. When Y is optionally substituted thiobenzyl the preparation is by reaction with HY.

[0031] The following Examples illustrate the invention.

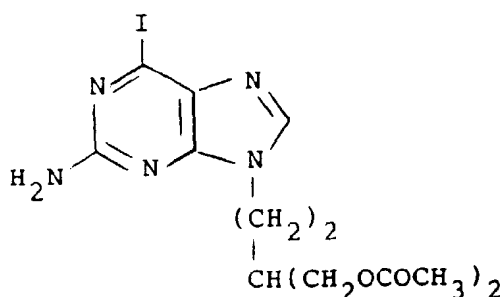
[0032] BRL 39123 and/or BRL 42810 may be prepared from the intermediates of Examples 2a), 3b), 4b), 5b), 6b), 7 and 8) according to the methods herein described.

[0033] When used therein, the Examples which incorporate the term '100 p.s.i', expressed in SI units is :  $6.895 \times 10^5 \text{ Nm}^{-2}$ .

#### Example 1

##### a) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodopurine

[0034]



#### Preparation 1

[0035] 2-Acetoxyethyl-4-iodobut-1-yl acetate (3.14g) was added to a stirred suspension of 2-amino-6-iodopurine (2.61g) and anhydrous potassium carbonate (2.08) in N,N-dimethylformamide (50cm<sup>3</sup>) and the resulting mixture stirred at ambient temperature for 18 hours. T.l.c. (5% methanol-dichloromethane) showed two products, *r<sub>f</sub>* = 0.24 and 0.47; corresponding to the N7- and N9-alkylated purines.

[0036] The reaction mixture was filtered and the residue washed with N,N-dimethylformamide (50cm<sup>3</sup>). Evaporation of the filtrate gave a pale coloured solid. Purification via column chromatography on silica (100g) [eluant 2.5% methanol-chloroform] gave the title compound 3.55g (79.4%) and 0.4g (8.9%) of the corresponding 7-isomer. m.p. (of title compound) 116-117°C

[0037] <sup>1</sup>H n.m.r. (D<sub>6</sub>DMSO): δ 1.90 (m, 3H, -CH<sub>2</sub>CH-), 2.0 (s, 6H, CH<sub>3</sub>-), 4.0(d, 4H-OCH<sub>2</sub>-), 4.10 (t, 2H, -NCH<sub>2</sub>-), 6.80 (brs, 2H -NH<sub>2</sub>), 8.15 (s, 1H, H-8).

#### Preparation 2

[0038] Using the above procedure 2-amino-6-iodopurine (3.8g) and 2-acetoxyethyl-4-bromobut-1-yl acetate (4.4g) gave the title compound 5.3g (81%, m.p. 116-117°C, and 0.5g (7.7%) of the corresponding N-7-alkylated purine.

[0039] <sup>1</sup>H n.m.r., t.l.c. and m.p. consistent with the title compound.

#### Preparation 3

[0040] A mixture 2-amino-6-iodopurine (1.5g), 2-acetoxyethyl-4-chlorobut-1-yl acetate (1.41g) and anhydrous potassium carbonate (1.19g) in N,N-dimethylformamide (40cm<sup>3</sup>) was stirred at 80°C overnight. When cool the pale yellow mixture was filtered and the filtrate evaporated under reduced pressure. Purification via column chromatography on silica (150g) [eluant 2% methanol-dichloromethane increasing to 4% methanol-dichloromethane] gave the title compound 2.08g (81%) and 0.136g (5.3%) of 7-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodopurine.

[0041] <sup>1</sup>H n.m.r., t.l.c. and m.p. consistent with the title compound.

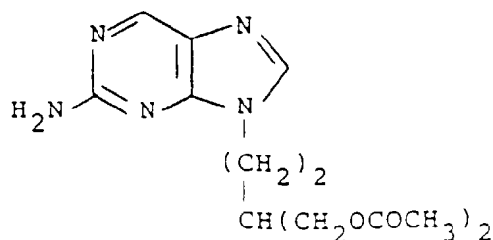
Preparation 4

**[0042]** Potassium bromide (6.3g) was added to a solution of 2-acetoxymethyl-4-methanesulphonyloxybut-1-yl acetate (10g) in N,N-dimethylformamide (87cm<sup>3</sup>) and the mixture stirred at 60-70° for 2 hours. The reaction mixture was cooled to ambient temperature and 2-amino-6-iodopurine (9.1g) and anhydrous potassium carbonate (7.3g) added. The resulting suspension was stirred at ambient temperature for 48 hours. T.l.c. (5% methanol-dichloromethane) showed two products, *r<sub>f</sub>*=0.24, and 0.47; corresponding to the N7- and N9-alkylated purines.

**[0043]** Filtration and evaporation of the filtrate gave a pale coloured residue that was partitioned between water (500cm<sup>3</sup>) and dichloromethane (500cm<sup>3</sup>). The layers were separated and the aqueous phase re-extracted with dichloromethane (2x250cm<sup>3</sup>). The combined organic extract was dried over magnesium sulphate and evaporated to give the crude product. Purification via silica gel chromatography (eluant 2% methanol-dichloromethane increasing to 3% methanol-dichloromethane) gave the title compound 12.2g (77%), m.p. 116-117°C and 0.8g (5%) of 7-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodopurine.

b) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-aminopurine, (BRL42810)

**[0044]**

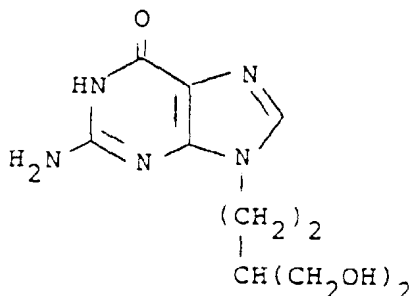


**[0045]** A solution of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodopurine (15.3g) and triethylamine (3.8cm<sup>3</sup>) in ethanol (200cm<sup>3</sup>) was hydrogenated over 5% palladium on charcoal (1.6g, Englehard type 4573) at 50° and 50 psi for 4 hours. The reaction mixture was filtered and residue washed with ethanol (200cm<sup>3</sup>). After evaporation of the filtrate to ca 50cm<sup>3</sup>, water (150cm<sup>3</sup>) and dichloromethane (75cm<sup>3</sup>) was added. The phases were separated and the aqueous layer extracted with dichloromethane (3x75cm<sup>3</sup>). The combined organic extract was dried over magnesium sulphate and evaporated to give the crude product. Recrystallisation from boiling butan-1-ol (30cm<sup>3</sup>) gave the title compound 9.8g (89%) m.p. 102°C

**[0046]** <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>) and t.l.c. (60:40 ethylacetate: methanol) were consistent with the title compound.

c) 9-(4-Hydroxy-3-hydroxymethylbut-1-yl)guanine, (BRL39123)

**[0047]**



**[0048]** A mixture of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodopurine (12g) and 2M-hydrochloric acid (266cm<sup>3</sup>) was stirred under reflux for 3 hours. After cooling, a solution of sodium hydroxide (36g) in water (72cm<sup>3</sup>) was added and the stirring continued at ambient temperature for 2 hours. The solution was neutralised with concentrated hydrochloric acid to precipitate the product. Recrystallisation from boiling water gave the title compound 6.0g (88%),



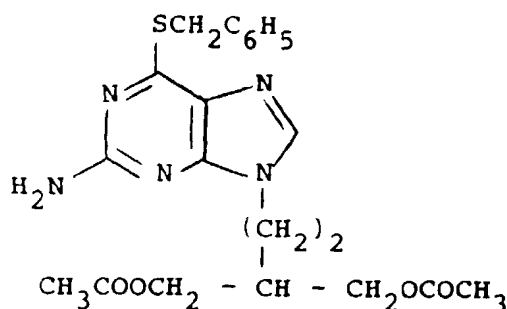
m.p. 278-280°C (dec.).

[0049]  $^1\text{H}$  n.m.r. ( $\text{D}_6\text{DMSO}$ ):  $\delta$  1.50 (m, 1H,  $-\text{CH}-$ ), 1.75 (q, 2H  $\text{CH}_2-\text{CH}$ ), 3.45 (m, 4H,  $-\text{CH}_2\text{OH}$ ), 4.05 (t, 2H,  $-\text{NCH}_2-$ ), 4.50 (t, 2H,  $-\text{CH}_2\text{OH}$ ), 6.50 (brs, 2H,  $-\text{NH}_2$ ), 7.75 (s, 1H,  $\text{H}-8$ ), 10.75 (brs, 1H,  $-\text{NHCO}$ ).

## Example 2

a) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(phenylmethyl)thio]purine

[0050]



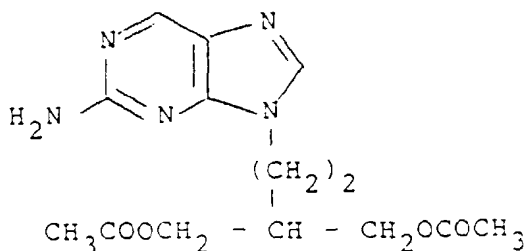
[0051] A mixture of 2-amino-6-[(phenylmethyl)thio]purine<sup>1</sup> (20g), 2-acetoxymethyl-4-iodobut-1-yl acetate (24.5g) and potassium carbonate (16.3g) in N,N-dimethylformamide (250  $\text{cm}^3$ ) was stirred at ambient temperature for 66 hours. T. l.c. (5% methanol-dichloromethane) showed two spots, rf 0.44, 0.74. The reaction mixture was filtered and the residue washed with N,N-dimethylformamide (100  $\text{cm}^3$ ). Evaporation of the filtrate gave a pale yellow viscous gum.

[0052] Purification via silica gel chromatography (eluant 5% methanol-dichloromethane) gave the title compound 30g (87%), rf (5% methanol-dichloromethane) = 0.74, as a viscous gum. A small amount of the corresponding N7-isomer 2.4g (7%) was also isolated, rf (5% methanol-dichloromethane) = 0.44.

$^1\text{H}$  n.m.r. ( $\text{CDCl}_3$ ):  $\delta$  1.85(m, 3H,  $-\text{CH}_2-\text{CH}-$ ), 2.05(s, 6H,  $\text{CH}_3$ ), 4.10(m, 6H,  $\text{NCH}_2 + \text{OCH}_2-$ ), 4.55(s, 2H,  $\text{CH}_2\text{C}_6\text{H}_5$ ), 5.15(brs, 2H,  $\text{NH}_2$ ), 7.25(m, 3H,  $\text{C}_6\text{H}_5$ ), 7.40(d, 2H,  $\text{C}_6\text{H}_5$ ), 7.65(s, 1H,  $\text{H}-8$ ).

b) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-aminopurine, (BRL 42810)

[0053]



[0054] Raney nickel (4g) was added to a solution of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(phenylmethyl)thio]purine (10g) in ethanol (250  $\text{cm}^3$ ) and the mixture treated with hydrogen (100 psi) at 100°C for 2 hours.

[0055] After filtration and washing of the residue with ethanol (250  $\text{cm}^3$ ) evaporation of the filtrate gave the crude material. Recrystallisation from butan-1-ol (10  $\text{cm}^3$ ) gave BRL 42810, 5.1g (70%), m.p. 102°C. This material was consistent with that prepared previously.

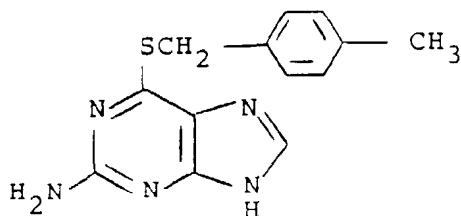
[0056]  $^1\text{H}$  n.m.r. ( $\text{CDCl}_3$ ):  $\delta$  1.90(m, 3H,  $-\text{CH}_2\text{CH}-$ ), 2.00(s, 6H,  $-\text{CH}_3$ ), 4.05 (d, 4H,  $\text{OCH}_2-$ ), 4.10(t, 2H,  $\text{NCH}_2-$ ), 5.35(brs, 2H,  $\text{NH}_2$ ), 7.70(s, 1H,  $\text{H}-8$ ), 8.60(s, 1H,  $\text{H}-6$ ).

<sup>1</sup> Prepared by the method of G.H. Hitchings et. al., US 3232938.

## Example 3

a) 2-Amino-6-[(4-methylphenyl)methylthio]purine

[0057]

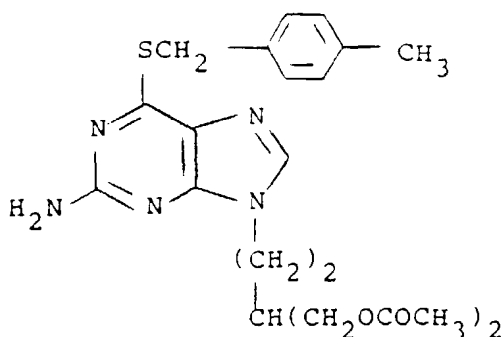


[0058] A mixture of thioguanine (25g),  $\alpha$ -chloro-p-xylene (21g) and potassium carbonate (30g) in N,N-dimethylformamide (500cm<sup>3</sup>) was stirred at ambient temperature overnight. The reaction mixture was filtered and the filtrate evaporated to give a yellow solid. Recrystallisation from methanol (100cm<sup>3</sup>) gave 25.7g (64%) of the title compound, m.p. 240-242°C

[0059] <sup>1</sup>H n.m.r. (D<sup>6</sup>DMSO):  $\delta$  2.25 (s, 3H, -CH<sub>3</sub>), 4.50 (s, 2H, SCH<sub>2</sub>-), 6.45 (brs, 2H, -NH<sub>2</sub>), 7.10 (d, 2H, C<sub>6</sub>H<sub>4</sub>-), 7.35 (d, 2H, C<sub>6</sub>H<sub>4</sub>), 7.90 (s, 1H, H-8), 12.55 (brs, 1H, >NH).

b) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(4-methylphenyl)methylthio]purine

[0060]

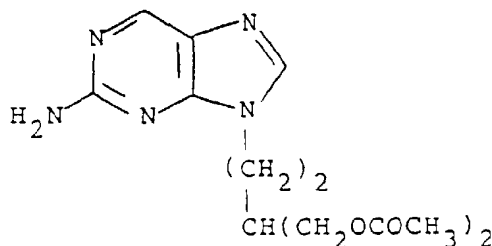


[0061] Using the previously described procedure 2-amino-6-[(4-methylphenyl)methylthio]purine (25g) and 2-acetoxymethyl-4-iodobut-1-yl acetate (29g) gave the title compound 33.3g (79%) m.p. 102-103°C, and 4.2g (9.9%) of 7-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(4-methylphenyl)methylthio]purine

[0062] <sup>1</sup>H n.m.r. (D<sup>6</sup>DMSO) of the title compound:  $\delta$  1.85 (m, 3H, -CH<sub>2</sub>CH<), 2.00 (s, 6H, CH<sub>3</sub>CO-), 2.25 (s, 3H, -CH<sub>3</sub>), 4.00 (d, 4H, -OCH<sub>2</sub>-), 4.10 (t, 2H, -NCH<sub>2</sub>), 4.50 (s, 2H, -SCH<sub>2</sub>), 6.60 (brs, 2H, -NH<sub>2</sub>), 7.10 (d, 2H, C<sub>6</sub>H<sub>4</sub>), 7.30 (d, 2H, C<sub>6</sub>H<sub>4</sub>), 7.95 (s, 1H, H-8).

c) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-purine, (BRL42810

[0063]



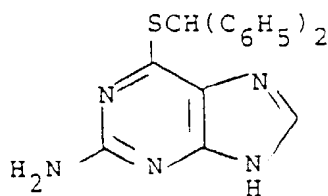
[0064] Raney nickel (3g) was added to a solution of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(4-methyl-phenyl)methylthio]purine (10g) in ethanol (250cm<sup>3</sup>) and the mixture treated with hydrogen at 100° and 100 psi for 40 hours. Filtration and evaporation of the filtrate gave the crude compound. Recrystallisation from butan-1-ol (18 cm<sup>3</sup>) gave the title compound 4.2g (60%). m.p. 100-102°C

[0065] <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>) and t.l.c (60:40 ethylacetate: methanol) were consistent with the title compound.

#### Example 4

a) 2-Amino-6-[(diphenylmethyl)thio]purine

[0066]

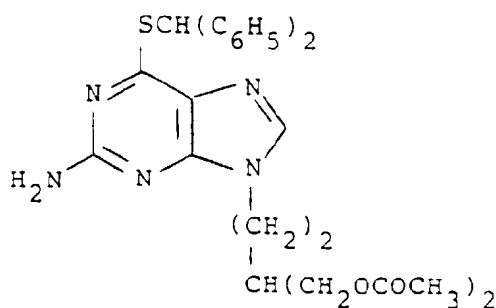


[0067] A mixture of thioguanine (25g), bromodiphenylmethane (37.1g) and potassium carbonate (31.1g) in N,N-dimethylformamide (250cm<sup>3</sup>) was stirred at ambient temperature for 66 hours. The reaction mixture was filtered and the filtrate evaporated to give a cream solid. Recrystallisation from methanol gave 24g (48%) of the title compound, m.p. 226-227°C

[0068] <sup>1</sup>H n.m.r. (D<sub>6</sub>DMSO): δ 6.35 (s, 2H, -NH<sub>2</sub>), 6.70 (s, 1H, SCH<), 7.30 (m, 6H, C<sub>6</sub>H<sub>5</sub>-), 7.50 (d, 4H, C<sub>6</sub>H<sub>5</sub>-), 7.90 (s, 1H, H-8), 12.50 (brs, 1H, >N-H).

b) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(diphenylmethyl)thio]purine

[0069]



[0070] A mixture of 2-amino-6-[(diphenylmethyl)thio]purine (6.7g), 2-acetoxymethyl-4-iodobut-1-yl acetate (7.0g) and anhydrous potassium carbonate (4.14g) in N,N-dimethylformamide (100cm<sup>3</sup>) was stirred at ambient temperature overnight. The reaction mixture was filtered and the residue washed with N,N-dimethylformamide (100cm<sup>3</sup>). Evaporation of the filtrate gave a pale coloured oil. Purification via column chromatography on silica (450g) [eluant 3% methanol-dichloromethane] gave the title compound 9.3g (89%) as a viscous gum and 1.1g (10.5%) of 7-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(diphenylmethyl)thio]purine.

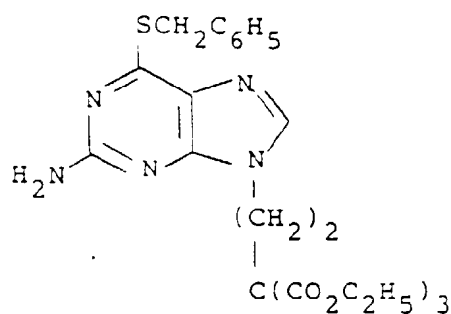
[0071] <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>) of the title compound δ 1.85 (m, 3H, -CH<sub>2</sub>CH<), 2.05 (s, 6H, CH<sub>3</sub>), 4.15 (d, 6H, -NCH<sub>2</sub>- + -OCH<sub>2</sub>-), 5.2 (s, 2H, -NH<sub>2</sub>) 6.2 (s, 1H, -SCH<) 7.25 (m, 6H, C<sub>6</sub>H<sub>5</sub>-), 7.5 (d, 4H, C<sub>6</sub>H<sub>5</sub>), 7.65 (s, 1H, H-8)

[0072] Mass spectrum of the title compound : m/e 519 (m<sup>+</sup>), main fragment ions at 277, 255, 199, 167 and 91.

#### Example 5

a) 2-Amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-[(phenylmethyl)thio]purine

[0073]

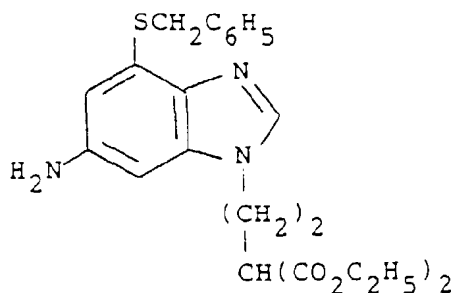


[0074] Ethyl 4-bromo-2,2-dicarboethoxybutanoate (14.5g) was added to a stirred suspension of 2-amino-6-[(phenylmethyl)thio]purine (11.4g) and anhydrous potassium carbonate (9.15g) in N,N-dimethylformamide (100cm<sup>3</sup>) and the resulting mixture stirred at 40° overnight. When cool the mixture was filtered and the filtrate evaporated to give a pale coloured viscous gum. Purification via silica gel chromatography (eluant dichloromethane increasing to 10% methanol-dichloromethane) gave 11.42g (50%) of the title compound, m.p. 100-102°. A second compound, 5.38g, was identified as 2-amino-9-(ethyl 2-carboethoxybutanoate-4-yl)-6-[(phenylmethyl)thio]purine, m.p. 86-88°. A mixed fraction containing 2.15g of the corresponding N7-substituted di- and tri- carboethoxybutanoates was also isolated.

[0075] <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>) of the title compound: δ 1.25(t, 9H, -CH<sub>3</sub>), 2.65(t, 2H, -CH<sub>2</sub>C-), 4.25 (m, 8H, -NCH<sub>2</sub>- + -CH<sub>2</sub>CH<sub>3</sub>), 4.55 (s, 2H, -SCH<sub>2</sub>-) 5.10(brs, 2H, -NH<sub>2</sub>). 7.25(m, 3H, C<sub>6</sub>H<sub>5</sub>-), 7.40 (d, 2H, C<sub>6</sub>H<sub>5</sub>-), 7.609(s, 1H, H-8).

b) 2-Amino-9-(ethyl 2-carboethoxybutanoate-4-yl)-6-[(phenylmethyl)thio]purine

[0076]



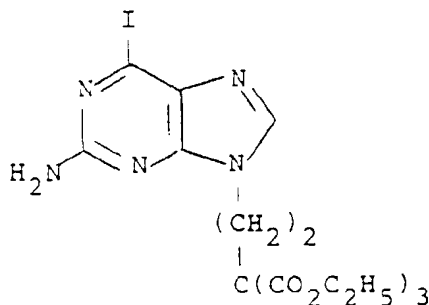
[0077] 2-Amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-[(phenylmethyl)thio]purine (3g) was added to a solution of sodium (0.4g) in ethanol (20cm<sup>3</sup>) and the mixture stirred at ambient temperature for 15 minutes. T.l.c. (2% methanol-dichloromethane), one-spot rf 0.40. The solution was neutralised with 2M-hydrochloric acid and water (100cm<sup>3</sup>) added. The mixture was extracted with dichloromethane (2 x 50 cm<sup>3</sup>) and the extract dried over magnesium sulphate. Filtration and evaporation of the filtrate gave the crude material. Purification via column chromatography on silica (40g) [eluant dichloromethane increasing to 5% methanol-dichloromethane] gave the title compound 1.2g (46.5%) as a viscous gum which slowly crystallised on standing at ambient temperature, m.p. 86-88°C.

[0078] <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>): δ 1.25 (t, 6H, CH<sub>3</sub>), 2.30 (m, 2H, CHCH<sub>2</sub>-), 3.20(t, 1H, CCHC), 4.00 (m, 6H, -NCH<sub>2</sub> + -CH<sub>2</sub>CH<sub>3</sub>), 4.40(s, 2H, SCH<sub>2</sub>-), 5.50 (brs, 2H, -NH<sub>2</sub>), 7.10(q, 3H, C<sub>6</sub>H<sub>5</sub>), 7.25 (d, 2H, C<sub>6</sub>H<sub>5</sub>-), 2.50 (s, 1H, H-8).

#### Example 6

a) 2-Amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-iodopurine

[0079]



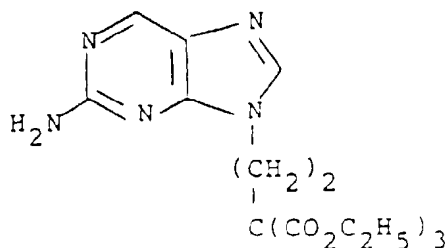
[0080] A mixture of 2-amino-6-iodopurine (10g), ethyl 4-bromo-2,2-dicarboethoxybutanoate (13g) and anhydrous potassium carbonate (8.0g) in N,N-dimethylformamide (150 cm<sup>3</sup>) was stirred at 40°C overnight. The mixture was filtered and the filtrate evaporated to leave a pale yellow solid. The solid was dissolved in 2% methanol-dichloromethane and column chromatographed on silica (200g) [eluant = 2% methanol-dichloromethane] to give the title compound 13.8g (69.4%) and 1.5g (7.5%) of 2-amino-7-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-iodopurine.

[0081] m.p. (of title compound) 99-102°C

[0082] <sup>1</sup>H n.m.r. (D<sup>6</sup>-DMSO) of title compound: δ 1.20(t, 9H, -CH<sub>2</sub>CH<sub>3</sub>), 2.60 (t, 2H, -CH<sub>2</sub>C-), 4.15(q, 6H, -CH<sub>2</sub>CH<sub>3</sub>), 4.50(t, 2H, N-CH<sub>2</sub>), 6.80(brs, 2H, -NH<sub>2</sub>), 8.00(s, 1H, H-8).

b) 2-Amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)purine

[0083]



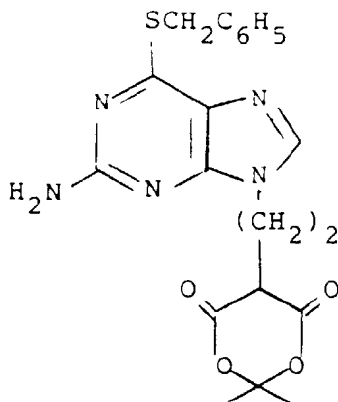
[0084] A mixture of 2-amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-iodopurine (85g), triethylamine (25.25 cm<sup>3</sup>) and 5% palladium on charcoal (10g) in ethanol (1,500 cm<sup>3</sup>) was hydrogenated at 100 psi and 50°C for 2 hours. T.l.c. (10% methanol-chloroform) showed one spot, *r<sub>f</sub>* = 0.40. When cool the mixture was filtered and the filtrate evaporated to leave a solid. The solid was dissolved in water (1000 cm<sup>3</sup>) and extracted with chloroform (3 x 500 cm<sup>3</sup>). The organic extracts were combined, dried over magnesium sulphate and evaporated to give the title compound 62.2g (96%) as an oil which crystallised on standing.

[0085] <sup>1</sup>H n.m.r. (D<sup>6</sup> -DMSO): 1.20(t,9H, -CH<sub>2</sub>CH<sub>3</sub>), 2.65(t,2H, -CH<sub>2</sub>C-), 4.15(q,6H, -CH<sub>2</sub>CH<sub>3</sub>), 4.35(t,2H, N-CH<sub>2</sub>), 6.50(brs, 2H, -NH<sub>2</sub>), 7.95(s, 1H, H-8), 8.65(s, 1H, H-6).

#### Example 7

2-Amino-9-[1-(2,2-dimethyl-1,3-dioxane-4,6-dione-5-yl) eth-2-yl]-6-[(phenylmethyl)thio]purine

[0086]



[0087] A mixture of 2-amino-6-[(phenylmethyl)thio]purine (1.0g), 2,2-dimethyl-1,3-dioxaspiro[2.5]octane-4,6-dione (0.7g) and potassium carbonate (1.0g) in dry N,N-dimethylformamide (10 cm<sup>3</sup>) was stirred at ambient temperature for 18 hours. The mixture was filtered and the filtrate evaporated. T.l.c. (20% methanol-dichloromethane) showed two products, *r<sub>f</sub>* = 0.3 and 0.1, corresponding to the potassium salts of the title compound and the N-7 isomer respectively. Proton n.m.r. evidence suggested a product ratio of 2.7:1.

[0088] The residue was dissolved in water, acidified to pH 4 with dilute hydrochloric acid and extracted with dichloromethane (2 x 100 cm<sup>3</sup>). The organic layers were combined, dried (magnesium sulphate) and evaporated to give a yellow solid.

[0089] Purification by column chromatography on silica [eluant = 5% methanol-dichloromethane] gave the title compound that was recrystallised from boiling ethyl acetate (0.2g, 12%).

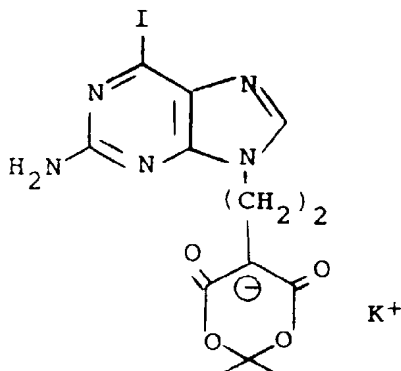
[0090]  $^1\text{H}$  n.m.r. ( $\text{D}^6\text{-DMSO}$ ):  $\delta$  1.68(s, 3H,  $-\text{CH}_3$ ), 1.83(s, 3H,  $-\text{CH}_3$ ), 2.39(m, 2H,  $\text{H-2'}$ ), 4.26(m, 2H,  $\text{H-1'}$ ), 4.50(m, 1H,  $\text{H-3'}$ ), 4.56(s, 2H,  $-\text{CH}_2\text{C}_6\text{H}_5$ ), 6.54(brs, 2H,  $-\text{NH}_2$ ), 7.19-7.49 (m, 5H,  $-\text{COH}_5$ ), 7.95(s, 1H,  $\text{H-8}$ ).

$\text{C}_{20}\text{H}_{21}\text{N}_5\text{O}_4\text{S}$	requires	C,56.19; H,4.95; N,16.38%
	found	C,55.97; H,4.94; N,16.04%

### Example 8

2-Amino-6-iodo-9-[1-(2,2-dimethyl-1,3-dioxane-4,6-dione-5-yl)eth-2-yl]purine potassium salt

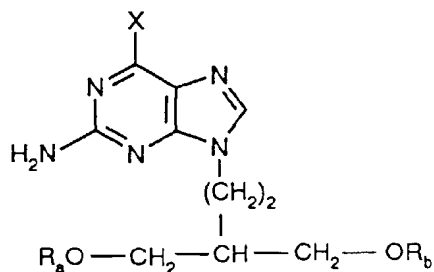
[0091]



[0092] A mixture of 2-amino-6-iodopurine (1.3g), 2,2-dimethyl-1,3-dioxaspiro[2.5]octane-4,6-dione (0.85g) and potassium carbonate (1.2g) in  $\text{N,N}$ -dimethylformamide ( $20\text{ cm}^3$ ) was stirred at ambient temperature for 18 hours. The mixture was filtered and the solvent evaporated. Proton n.m.r. spectroscopy suggested a mixture of the title compound and 2-amino-6-iodo-7-[1-(2,2-dimethyl-1,3-dioxane-4,6-dione-5-yl)eth-2-yl]purine potassium salt in the ratio of 2.8:1.  $^1\text{H}$  n.m.r. ( $\text{D}^6\text{-DMSO}$ ): of the title compound:  $\delta$  1.40(s, 6H,  $-\text{CH}_3$ ), 2.64(t, 2H,  $\text{H-2'}$ ), 4.04(t, 2H,  $\text{H-1'}$ ), 6.75(brs, 2H,  $-\text{NH}_2$ ), 7.96(s, 1H,  $\text{H-8}$ ).

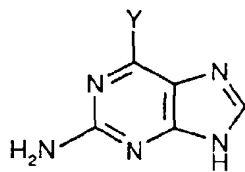
### Claims

1. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



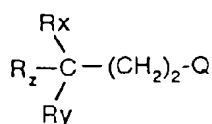
(I)

wherein X is hydrogen or hydroxy and  $\text{R}_a$  and  $\text{R}_b$  are independently hydrogen or a group  $\text{RCO-}$  wherein R is phenyl or  $\text{C}_{1-18}$  alkyl;  
which process comprises reacting a compound of formula (II):



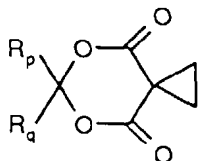
(II)

wherein the amino group is optionally protected, Y is iodo, diphenylmethylthio or benzylthio wherein the phenyl moiety is optionally substituted by one or two groups selected from C<sub>1-4</sub> alkyl, halo and C<sub>1-4</sub> alkoxy, with a compound of formula (III):



(III)

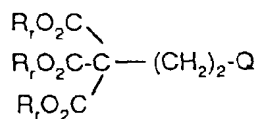
wherein Q is a leaving group; Rx and Ry are protected hydroxymethyl or acyloxymethyl, or group(s) convertible to hydroxymethyl or acyloxymethyl; and Rz is hydrogen or a group convertible thereto; or a compound of formula (IIIA):-



(IIIA)

wherein Rp and Rq are independently hydrogen, C<sub>1-6</sub> alkyl or phenyl, or Rp and Rq together are C<sub>4-6</sub> polymethylene; and thereafter converting Y to X is hydroxy by means of hydrolysis, or to X is hydrogen by means of reduction; converting Rx and Ry, when other than hydroxymethyl or acyloxymethyl, to hydroxymethyl or acyloxymethyl; optionally converting Rx/Ry hydroxymethyl to acyloxymethyl or vice versa; deprotecting the 2-amino group where necessary; converting Rz, when other than hydrogen, to hydrogen; and optionally forming a pharmaceutically acceptable salt thereof.

2. A process according to claim 1 wherein the compound of formula (III) is of formula (IIIB):

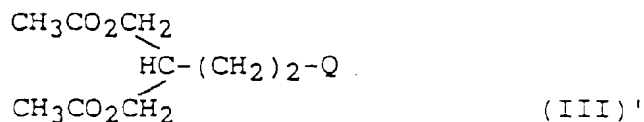


(IIIB)



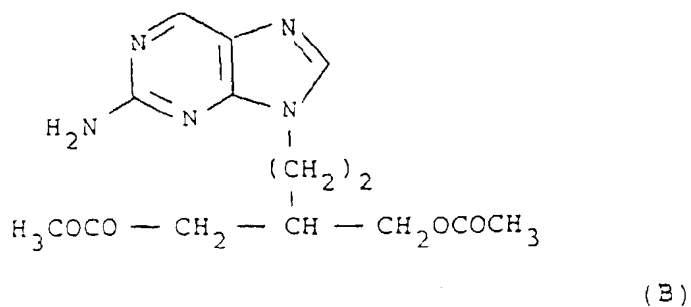
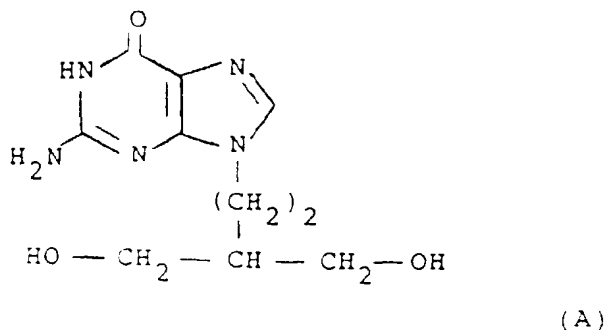
wherein  $R_1$  is  $C_{1-6}$  alkyl or phenyl  $C_{1-6}$  alkyl, in which any phenyl moieties are optionally substituted by one or two groups selected from  $C_{1-4}$  alkyl, halo and  $C_{1-4}$  alkoxy.

3. A process according to claim 1 wherein the compound of formula (III) is of formula (III)':

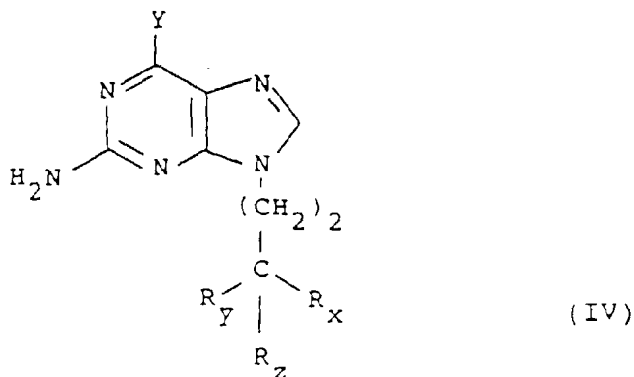


wherein Q is a leaving group.

4. A process according to claim 1, 2 or 3 wherein Y is iodo.
5. A process according to any one of claims 1 to 4 wherein Q is halo, tosyloxy or mesyloxy.
6. A process according to any one of claims 1 to 5 for the preparation of a compound of formula (A) or (B):



7. An intermediate of formula (IV):

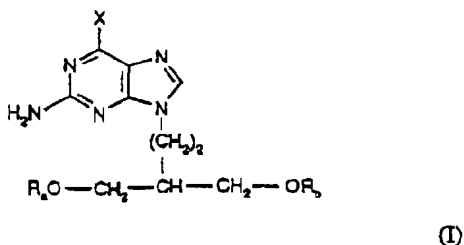


wherein Y, Rx, Ry and Rz are as defined in claim 1.

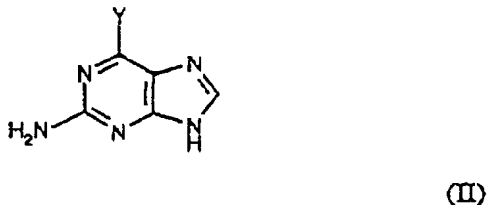
8. 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodopurine,  
 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(phenylmethyl)thio]purine,  
 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(4-methylphenyl)methylthio]purine,  
 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(diphenylmethyl)thio]purine,  
 2-amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-[(phenylmethyl)thio]purine,  
 2-amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-iodopurine,  
 2-amino-9-[1-(2,2-dimethyl-1,3-dioxane-4,6-dione-5-yl)eth-2-yl]-6-[(phenylmethyl)thio]purine,  
 2-amino-6-iodo-9-[1-(2,2-dimethyl-1,3-dioxane-4,6-dione-5-yl)eth-2-yl]purine potassium salt, or  
 9-[(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(phenacylmethyl)thio]purine.

## Patentansprüche

1. Verfahren zur Herstellung einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon:

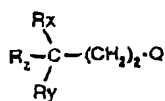


worin X ein Wasserstoffatom oder eine Hydroxylgruppe bedeutet und Ra und Rb unabhängig Wasserstoffatome oder Reste RCO- bedeuten, worin R eine Phenylgruppe oder einen C1-18-Alkylrest bedeutet; wobei das Verfahren umfaßt: Umsetzung einer Verbindung der Formel (II):



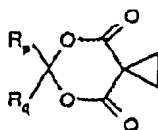
worin die Aminogruppe gegebenenfalls geschützt ist, Y ein Iodatom, eine Diphenylmethylthio- oder Benzylthio-

gruppe bedeutet, worin die Phenyleinheit gegebenenfalls mit einem oder zwei aus C<sub>1-4</sub>-Alkylresten, Halogenatomen und C<sub>1-4</sub>-Alkoxyresten ausgewählten Resten substituiert ist, mit einer Verbindung der Formel (III):



(III)

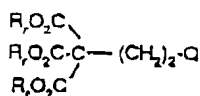
worin Q eine Abgangsgruppe bedeutet; R<sub>x</sub> und R<sub>y</sub> geschützte Hydroxymethyl- oder Acyloxymethylgruppen oder (einen) in eine Hydroxymethyl- oder Acyloxymethylgruppe überführbare(n) Rest(e) bedeuten; und R<sub>z</sub> ein Wasserstoffatom oder einen hierzu überführbaren Rest bedeutet; oder einer Verbindung der Formel (III A):



(III A)

worin R<sub>p</sub> und R<sub>q</sub> unabhängig Wasserstoffatome, C<sub>1-6</sub>-Alkylreste oder Phenylgruppen bedeuten oder R<sub>p</sub> und R<sub>q</sub> zusammen einen C<sub>4-6</sub>-Polymethylenrest bedeuten; und anschließend Überführen von Y in X = eine Hydroxylgruppe mittels Hydrolyse oder in X = ein Wasserstoffatom mittels Reduktion; Überführen von R<sub>x</sub> und R<sub>y</sub>, wenn sie von Hydroxymethyl- oder Acyloxymethylgruppen verschieden sind, in Hydroxymethyl- oder Acyloxymethylgruppen; gegebenenfalls Überführen von R<sub>x</sub>/R<sub>y</sub> = Hydroxymethylgruppen in Acyloxymethylgruppen oder umgekehrt; Entfernung der Schutzgruppe von der 2-Aminogruppe, falls nötig; Überführen von R<sub>z</sub>, wenn es von Wasserstoff verschieden ist, in ein Wasserstoffatom; und gegebenenfalls Herstellung eines pharmazeutisch verträglichen Salzes davon.

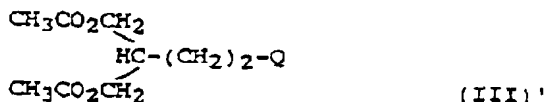
2. Verfahren nach Anspruch 1, wobei die Verbindung der Formel (III) die Formel (III B) aufweist:



(III B)

worin R<sub>r</sub> einen C<sub>1-6</sub>-Alkyl- oder Phenyl-C<sub>1-6</sub>-alkylrest bedeutet, worin jede der Phenyleinheiten gegebenenfalls mit einem oder zwei aus C<sub>1-4</sub>-Alkylresten, Halogenatomen und C<sub>1-4</sub>-Alkoxyresten ausgewählten Resten substituiert ist.

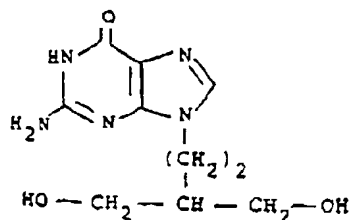
3. Verfahren nach Anspruch 1, wobei die Verbindung der Formel (III) die Formel (III)' aufweist:



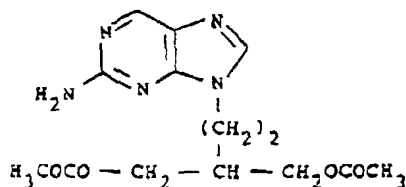
worin Q eine Abgangsgruppe bedeutet.

4. Verfahren nach Anspruch 1, 2 oder 3, wobei Y ein Iodatom bedeutet.

5. Verfahren nach einem der Ansprüche 1 bis 4, wobei Q ein Halogenatom, eine Tosyloxy- oder Mesyloxygruppe bedeutet.
6. Verfahren nach einem der Ansprüche 1 bis 5 zur Herstellung einer Verbindung der Formel (A) oder (B):

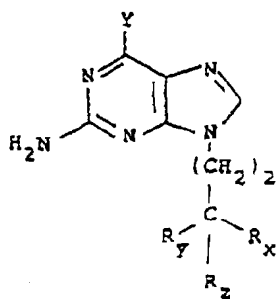


(A)



(B)

7. Intermediärverbindung der Formel (IV):



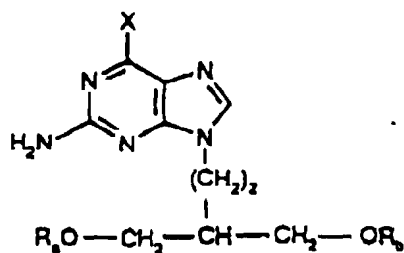
(IV)

worin Y, Rx, Ry und Rz wie in Anspruch 1 definiert sind.

8. 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodpurin,  
 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(phenylmethyl)thio]purin,  
 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(4-methylphenyl)methylthio]purin,  
 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(diphenylmethyl)thio]purin,  
 2-Amino-9-(ethyl-2,2-dicarboethoxybutanoat-4-yl)-6-[(phenylmethyl)thio]purin,  
 2-Amino-9-(ethyl-2,2-dicarboethoxybutanoat-4-yl)-6-iodpurin,  
 2-Amino-9-[1-(2,2-dimethyl-1,3-dioxan-4,6-dion-5-yl)eth-2-yl]-6-[(phenylmethyl)thio]purin,  
 2-Amino-6-iod-9-[1-(2,2-dimethyl-1,3-dioxan-4,6-dion-5-yl)eth-2-yl]purin-Kaliumsalz, oder  
 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(phenacylmethyl)thio]purin.

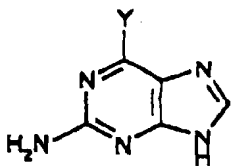
## Revendications

1. Procédé de préparation d'un composé de formule (I) ou d'un sel pharmaceutiquement acceptable de celui-ci :



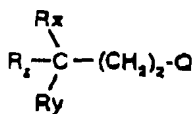
(I)

où X est un hydrogène ou un hydroxy et  $R_a$  et  $R_b$  sont indépendamment un hydrogène ou un groupe  $RCO-$ , dans lequel R est un phényle ou un alkyle en  $C_{1-18}$  ;  
lequel procédé comprend la réaction d'un composé de formule (II) :



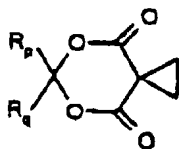
(II)

dans laquelle le groupe amino est éventuellement protégé, Y est un iodo, un diphenylméthylthio ou un benzylthio dans lequel le groupement phényle est éventuellement substitué par un ou deux groupes choisis parmi un alkyle en  $C_{1-4}$ , un halogéno et un alcoxy en  $C_{1-4}$ , avec un composé de formule (III) :



(III)

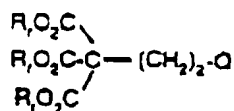
dans laquelle Q est un groupe partant ;  $R_x$  et  $R_y$  sont un hydroxyméthyle ou acyloxyméthyle protégé, ou un (des) groupe(s) pouvant être transformé(s) en un hydroxyméthyle ou acyloxyméthyle ; et  $R_z$  est un hydrogène ou un groupe pouvant être transformé en celui-ci ; ou un composé de formule (IIIA) :



(IIIA)

dans laquelle  $R_p$  et  $R_q$  sont indépendamment un hydrogène, un alkyle en  $C_{1-6}$  ou un phényle, ou  $R_p$  et  $R_q$  sont conjointement un polyméthylène en  $C_{4-6}$  ; et ensuite la transformation de Y en X = hydroxy par hydrolyse, ou en X = hydrogène par réduction ; la transformation de  $R_x$  et  $R_y$ , lorsqu'ils sont différents d'un hydroxyméthyle ou d'un acyloxyméthyle, en un hydroxyméthyle ou un acyloxyméthyle ; éventuellement la transformation de  $R_x/R_y$  hydroxyméthyle en acyloxyméthyle ou vice versa ; la déprotection du groupe 2-amino lorsque cela est nécessaire ; la transformation de  $R_z$ , lorsqu'il est différent d'un hydrogène, en hydrogène ; et éventuellement la formation d'un sel pharmaceutiquement acceptable de celui-ci.

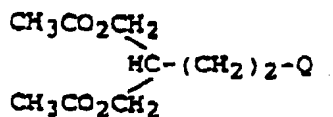
2. Procédé selon la revendication 1, dans lequel le composé de formule (III) et de formule (IIIB) :



(IIIB)

dans laquelle  $R_1$  est un alkyle en  $C_{1-6}$  ou un phényl- $C_{1-6}$ -alkyle, dans lequel tous groupements phényle sont éventuellement substitués par un ou deux groupes choisis parmi un alkyle en  $C_{1-4}$ , un halogéno et un alcoxy en  $C_{1-4}$ .

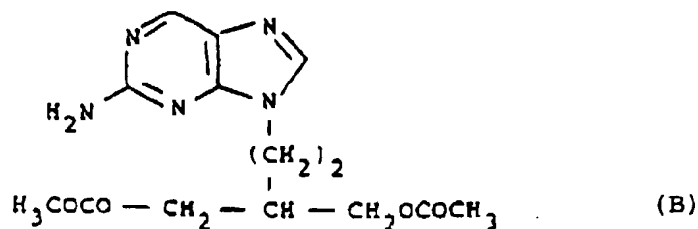
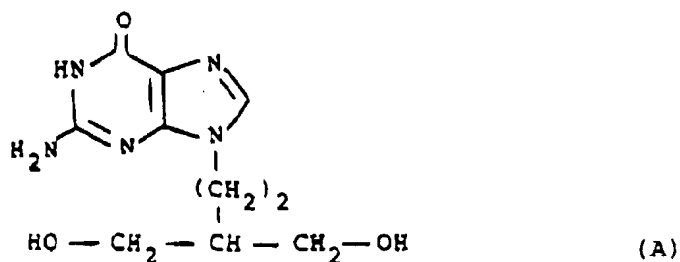
3. Procédé selon la revendication 1, dans lequel le composé de formule (III) est de formule (III)' :



(III)'

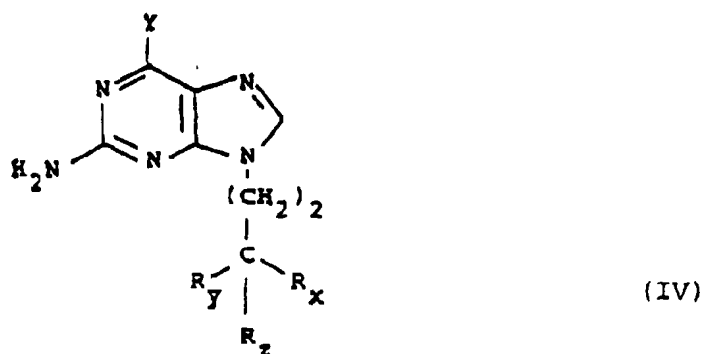
dans laquelle Q est un groupe partant.

4. Procédé selon la revendication 1, 2 ou 3, dans lequel Y est un iodo.
5. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel Q est un halogéno, un tosyloxy ou un métyloxy.
6. Procédé selon l'une quelconque des revendications 1 à 5, destiné à la préparation d'un composé de formule (A) ou (B) :



25

7. Intermédiaire de formule (IV) :



40

dans laquelle Y, R<sub>x</sub>, R<sub>y</sub> et R<sub>z</sub> sont tels que définis à la revendication 1.

8. 9-(4-acétoxy-3-acétoxyméthylbut-1-yl)-2-amino-6-iodopurine,  
 9-(4-acétoxy-3-acétoxyméthylbut-1-yl)-2-amino-6-[(phénylméthyl)thio]purine,  
 9-(4-acétoxy-3-acétoxyméthylbut-1-yl)-2-amino-6-[(4-méthylphényl)méthylthio]purine,  
 9-(4-acétoxy-3-acétoxyméthylbut-1-yl)-2-amino-6-[(diphénylméthyl)thio]purine,  
 2-amino-9-(éthyl 2,2-dicarboéthoxybutanoate-4-yl)-6-[(phénylméthyl)thio]purine,  
 2-amino-9-(éthyl 2,2-dicarboéthoxybutanoate-4-yl)-6-iodopurine,  
 2-amino-9-[1-(2,2-diméthyl-1,3-dioxane-4,6-dione-5-yl)éth-2-yl]-6-[(phénylméthyl)thio]purine,  
 sel de potassium de 2-amino-6-iodo-9-[1-(2,2-diméthyl-1,3-dioxane-4,6-dione-5-yl)éth-2-yl]-purine, ou  
 9-((4-acétoxy-3-acétoxyméthylbut-1-yl)-2-amino-6-[phénacilméthyl)thio]purine.